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TRIGGERABLE DELIVERY SYSTEM FOR PHARMACEUTICAL AND NUTRITIONAL COMPOUNDS AND METHODS OF UTILIZING SAME

Related Applications

This application is a Continuation in Part and claims priority to U.S. Patent Application Serial Number 10/325,474 filed on December 20, 2002 in the names of Jason Lye and Gavin MacDonald (and referenced by attorney docket number 18,113). U.S. Patent Application Serial Number 10/325,474 is incorporated by reference herein it its entirety.

Technical Field

This invention relates to delivery systems for pharmaceutical materials. More specifically, this invention relates to delivery systems and methods of delivering various pharmaceutical materials into or onto a patient's body.

Background Of The Invention

A delivery system generally refers to a system that aids or otherwise facilitates the delivery of a functional material to a desired location. The functional material can be any material that acts upon a substrate or otherwise provides a benefit once delivered to the desired location. Examples of functional materials that may benefit from the use of a delivery system include pharmaceuticals that are intended to be ingested, transferred transdermally, or subcutaneously injected into a human or animal patient's body, vitamins and nutrients (nutritional materials), and various other and numerous additives that can similarly be introduced into the body of a patient.

Even in view of recent advances in the art of delivery systems, further improvements in delivery systems for pharmaceutical and nutritional functional

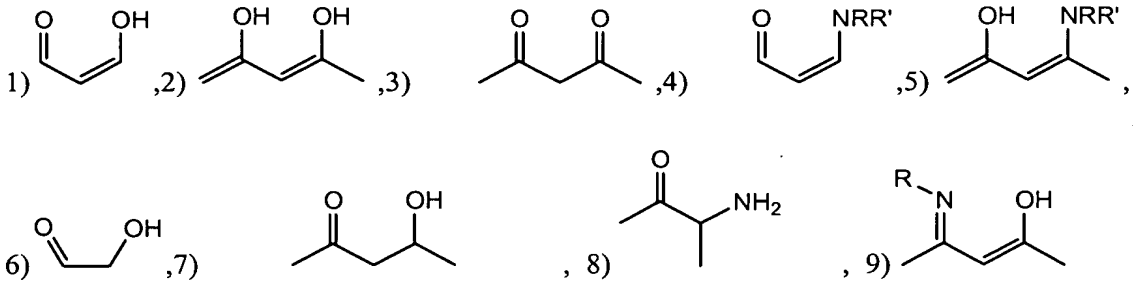
materials are still needed. For example, a need currently exists for a delivery system that can bind to various functional materials that does not incorporate relatively expensive chemical formulations or that does not require any complex process steps for incorporating a functional material into the delivery system. With respect to pharmaceutical and nutritional materials, a need also exists in the art for a delivery system for such materials that is capable of affixing the pharmaceutical or other health -related compounds to the delivery system, but will readily release such pharmaceutical materials or other health-related compounds upon the occurrence of a selected event or trigger. A need also exists for a method for selectively triggering the release of a pharmaceutical material or other health-related compound where and when it is needed. It is to such needs that the current invention is directed.

Summary Of The Invention

The present invention is generally directed to a delivery system for various functional materials. The functional materials can be, for instance, health-related compounds/materials such as pharmaceuticals, anti-microbial agents, anti-viral agents, antibiotics, xenobiotics, nutriceutical agents (nutritional materials), signal agents, combinations of such, and the like. In accordance with one embodiment of the present invention, the functional materials are adsorbed onto alumina that is contained in or on a particle, and desirably a nanoparticle. Nanoparticles are particularly desirable for the large surface area they offer and the potential exposure of the functional agent to body tissue. The resulting carrier particles can then be used as is or can be combined with a vehicle, such as a liquid vehicle, to deliver the functional material to a desired location within or on a patient's body. For example, when the functional material is a pharmaceutical, the particles making up the delivery system of the present invention, can be incorporated into a liquid vehicle and either ingested, applied subcutaneously, or applied topically to the skin of a patient using any conventional application means. The pharmaceutical may then be selectively released from the carrier particle (such as an alumina, silica, or alumina coated silica particle) so as to release the pharmaceutical at a targeted/desirable body location, or at a desirable moment. In

one embodiment, such selective release can be accomplished by exposure of the particle to a change in environmental condition, such as a pH change. For example, such selective release may be accomplished by exposure to an alkaline environment. Alternatively, such selective release may be accomplished by exposure to an acidic environment. Still further, such selective release may be the result of exposure of the carrier particle to particular chemical stimuli. In an alternative embodiment of the invention, a method for applying a health related compound utilizes a health-related compound coated particle, and selectively releasing the compound upon exposure of the particle to either a change in environmental condition, or upon exposure to a chemical stimulus.

Thus, in one embodiment, the present invention is directed to a particle containing alumina. At least a portion of the alumina contained by the particle is present on a surface of the particle. A functional compound is bonded to the alumina on the surface of the particle. The functional compound prior to bonding with the alumina contains a moiety comprising one or more of:



a tautomer thereof, or a functional equivalent thereof and wherein R and R' comprise independently hydrogen, an alkyl group, or an aryl group.

The above moieties can be present as is on a functional compound. Alternatively, however, each of the above moieties can include further R groups attached to the carbon chain shown above. In general, any such R group can appear in association with the above moieties as long as the R group does not interfere with the bonding of the moiety to an alumina particle. The above moieties have been found to form a bond with alumina in constructing the compositions of the present invention.

The functional compounds can then in one embodiment, be selectively released in either a basic or acidic environmental condition. For instance, in one

specific embodiment of the invention, the functional compounds can be released in the basic/alkaline environment of a vagina experiencing a yeast infection. In a second embodiment, the functional compounds can be released in the basic environment of the small intestine so as to treat an infection, after passing through the acidic environment of the stomach. In still a further alternative embodiment, a functional compound may be released as a result of environmental stimuli as an alert or in conjunction with the completion of the delivery of a pharmaceutical material so as to provide indication of such delivery or the success of such treatment. Such indicator or signal may be in the form of a dye or fragrance.

In still a further alternative embodiment, such signal may be the result of a functional material contained on a first type of particle, and such coated particle may be included with additional particles of a different variety, that contain health related compounds. In still a further alternative embodiment, the functional material may be released in response to a particular chemical stimuli, which is intentionally applied to the site of the carrier particles. In still a further alternative embodiment, a method of utilizing a triggerably releasable delivery system in the treatment of a patient's body includes the steps of providing at least one type of particle selected from alumina particles, alumina covered particles, and silica particles; adsorbing at least one functional compound to the surface of the particle or particles to form at least a partially coated particle or particles; exposing the at least partially coated particle or particles to a patient's body such as by ingestion, injection, transdermal transfer or transmucosal transfer; and exposing the particle or particles to an environmental or chemical condition whereby the health related compound is released from the surface of the particle to the patient's body.

Other features and aspects of the present invention are discussed in greater detail below.

Brief Description of the Drawings

Figure 1 illustrates an exploded perspective view of a transdermal drug delivery device in accordance with the invention.

Figure 2 illustrates a cross-sectional view of the transdermal delivery device of Fig. 1.

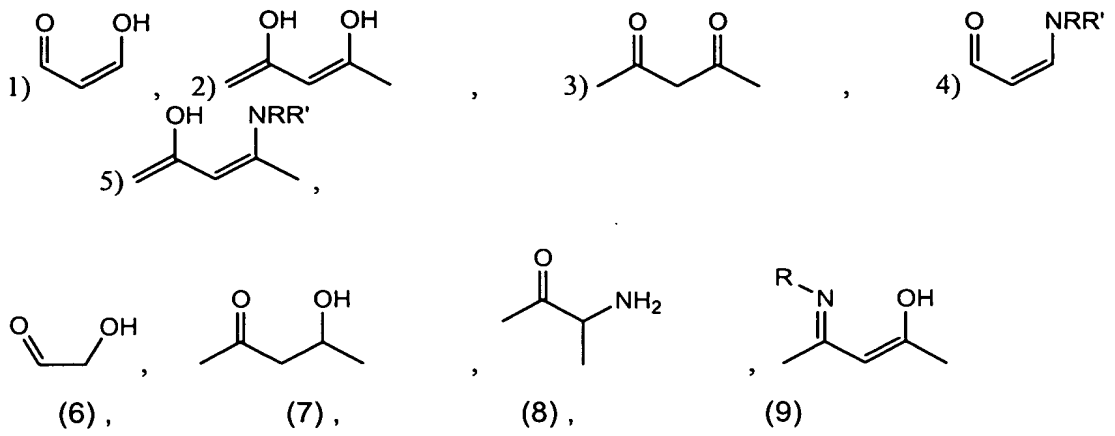
Detailed Description

In general, the present invention is directed to a triggerable delivery system for functional compounds and methods of using the same. Functional compounds can be any pharmaceutical and/or nutritionally suitable substance that can provide a benefit to a location on or within a patient's body once delivered. For the purposes of this application, it should be understood that the term "patient" refers to both human and non-human patients. Desirably, such functional materials are health related compounds such as pharmaceutical or nutritional materials.

In accordance with one embodiment of the present invention, the delivery system is generally directed to the construction of a particle containing alumina and use of such particle to selectively deliver functional compounds contained on the particle upon the occurrence/exposure of a triggering mechanism. The particle acts as a carrier for a functional compound.

Specifically, the alumina contained within the particle provides a bonding site on the surface of the particle for a functional compound. The functional compound (the pharmaceutical, nutritional material, or other health related material cited herein) becomes adsorbed onto the surface of the alumina. Once the functional compound is bonded to the alumina, the resulting particle can then be used to deliver the functional compound to a particular location within, or on a body. The particles can be used as is, for instance, or can be combined with a liquid, gel or other vehicle which may facilitate delivery of the particles depending upon the particular application. Such liquid and gel vehicles are known to those skilled in the art. The particles and/or vehicle can also be used in conjunction with a drug delivery apparatus, such as a modified bandage or modified tampon. Such a bandage or tampon would be modified to include either the particles themselves or a vehicle containing the particles.

Functional compounds that are well suited for use in the present invention include compounds that contain at least one of the following moieties:



a tautomer thereof, or a functional equivalent thereof and wherein R and R' comprise independently hydrogen, an alkyl group, or an aryl group. As used herein, a functional equivalent to one of the above moieties refers to functional materials that include similar reactive groups as shown above, but which are not positioned on a molecule exactly as shown above and yet will still bond with alumina in a similar manner.

Referring to the moieties shown above, moiety (1) may be considered a carboxy-hydroxy moiety. Moiety (2) may be considered a hyrdoxy-hydroxy moiety, while moiety (3) may be considered a carboxy-carboxy moiety. Moieties (4) and (5), on the other hand, can be considered vinylalogous amide moieties. In moieties (4) and (5) above, the amine groups can be primary amines, secondary amines, or tertiary amines. Moieties (6) and (7) may be considered hydroxyl carbonyl moieties. Moiety (8) may be considered a carboxy amine. Moieties such as (8) may be found in amino acids. Moiety (9) may be considered a hydroxy imine. In general, any suitable functional compound containing one of the above moieties or a functional equivalent thereof may be used in accordance with the present invention. Further, it should be understood that various additional R groups may be included with the above moieties as long as the R groups do not interfere with the bond that is formed with alumina.

The above moieties may form a relatively strong bond to an alumina surface. Without wishing to be bound by theory, it is believed that the above moieties form a bidentate ligand bonding system with alumina surfaces. For instance, it is believed that alumina forms a covalent bond and a coordinate bond

with the above moieties. Further, it is believed that a surface reaction occurs causing the functional compound to remain on the surface of the particle (unless triggerably released) and form a coating thereon. The functional material can cover the entire resulting particle or can be located at particular locations on the particle. Further, it should be understood that the particles of the present invention can contain more than one functional compound so as to deliver multiple treatments to address either a patient's multiple symptoms or a patient's multiple conditions.

Of particular advantage, in many embodiments, it has also been discovered that a functional compound can be bonded to alumina without significantly impacting the positive surface charge of alumina, which can be measured as zeta potential. The term "zeta potential" is used herein to mean without limitation, a potential gradient that arises across an interface. This term especially refers to the potential gradient that arises across the interface between the Stern layer in contact with the particle of the present invention and the diffuse layer surrounding the particle. Zeta potential measurements can be taken using, for instance, a Zetapals instrument which is available from the Brookhaven Instrument Corporation of Holtsville, New York. For example, zeta potential measurements can be conducted by adding one to three drops of a sample into a cuvet containing 1 mM KCl solution, and using the instrument's default functions preset for aqueous solutions.

Thus, once alumina is bonded to the functional material, the resulting molecule continues to maintain a relatively strong positive charge. For instance, particles made according to the present invention can have a zeta potential of greater than 20 mV, particularly greater than 30 mV, and, in some embodiments, greater than 40 mV. By remaining positively charged, the particles are well suited for being affixed to substrates that carry a negative surface charge through coulombic attraction. Depending upon the difference in charge between the particle of the present invention and the surface of a substrate, the bond of the particle in some applications can be relatively permanent and substantive. Consequently, the delivery system of the present invention can be used to affix functional compounds to various substrates without the use of chemical binders or other attachment structures. As an example, the carrier particle (delivery system)

can include along its surface a pharmaceutical functional compound, and yet the particle may still retain sufficient positive charge, to allow it to be attached to a negatively charged bandage or other topically contacting substrate layer. Then upon the occurrence of a specific chemical or environmental stimuli, the functional material contained on the particle can be selectively released to the body of a patient, but the carrier particles will remain affixed to the bandage or other charged surface.

Various different particles and compositions can be used in the present invention. For instance, alumina or silica particles may be used, depending upon the functional compound and the trigger for releasing it. Silica particles are available under the designation SNOWTEX-C through from Nissan Chemical America (Houston , TX). Various different particles and compositions that contain alumina can be used in the present invention. For example, in one embodiment, the functional material is combined with an alumina sol. Many different types of alumina sols are commercially available with varying particle size. Of particular advantage, alumina sols can be prepared that carry a relatively strong positive surface charge or zeta potential. In this embodiment, the particle that is reacted with the functional compound contains primarily and in some embodiments exclusively alumina. Examples of alumina particle materials, include Aluminasol-100, and Aluminasol-200, available from Nissan Chemical America (Houston , TX).

In other embodiments, however, the alumina particle reacted with the functional compound can contain various other ingredients. In general, the particle can contain any material that does not adversely interfere with the ability of the functional material to bond to alumina. In this regard, at least a portion of the alumina contained by the particle should be present on the surface of the particle so that the alumina is available for adsorbing the functional compound.

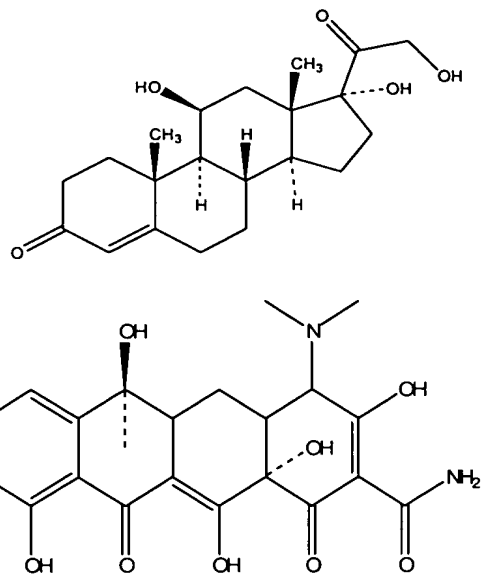
In one particular embodiment of the present invention, the particle can contain a core material coated with alumina. The alumina can form a continuous coating over the particle or a discontinuous coating. The core material can be, for instance, an inorganic oxide, such as silica. For example, in one embodiment, sols can be used that contain silica nanoparticles that have an alumina surface coating. Such sols are currently commercially available, for instance, from Nissan Chemical America of Houston, Texas. The silica is coated with alumina to provide stability to

the sols over certain pH ranges. In fact, alumina coated silica sols may have greater stability in some applications of the present invention in comparison to alumina sols. A specific example of alumina particle materials with silica cores, include Snowtex-AK, available from Nissan Chemical America, Houston, TX) and Ludox CI from Grace Davison, Columbia, MD.

As described above, any suitable pharmaceutical and/or nutritional functional compound containing one of the above moieties, a tautomer thereof, or a functional equivalent thereof may be used in accordance with the present invention. Examples of functional compounds include pharmaceuticals, and xenobiotics. Xenobiotics is a general term used to describe any chemical interacting with an organism that does not occur in the normal metabolic pathways of that organism. Other functional compounds can include therapeutic agents, nutriceutical (nutritional)agents, anti-viral agents, anti-microbial agents, and the like. For the purposes of this application, the terms "functional compound or functional agent" shall be taken to include "health –related compounds" which shall encompass pharmaceuticals, nutritional compounds, xenobiotics, anti-microbial agents, anti-viral agents, therapeutic agents and signal agents.

One example of a therapeutic agent that may be used in the present invention is hydrocortisone. Hydrocortisone is a natural anti- inflammatory hormone of the glucocorticoid family of hormones produced by the adrenal cortex. Examples of nutritional compounds include ascorbic acid and aspartame. In one particular embodiment, the functional compound may be a pharmaceutical/anti-microbial agent such as an antibiotic. An example of such an antibiotic may include tetracycline. Tetracycline is an antibiotic substance produced by Streptomyces spp. Hydrocortisone and tetracycline structural formulas are provided below:

Structure of Hydrocortisone (Type 6 moiety)



Structure of Tetracycline (Type 1 and 3 moieties)

As can be seen by the above structural formula, tetracycline is an antibacterial agent that contains a carbonyl-hydroxy functionality, capable of bonding with alumina in accordance with the present invention. Tetracycline is a series of isomers of cyclomycin.

In still a further alternative embodiment, a signal agent, such as a fragrance, may be used by itself or in conjunction with a health related compound on a variety of particle types to both treat a condition, and also to provide an indication to the patient of the effectiveness of such treatment or the occurrence of a particular event. As an example, a fragrance may be adsorbed to one type of particle and an antibiotic may be adsorbed to a second type of particle. The particles can be delivered to an infected site simultaneously. If the infected site is alkaline, it will prompt the release of the antibiotic. Upon removal of the infection, and the return to a more normal acidic environment, the fragrance may be released, thereby providing an indication of the effective treatment of the infection. In a further example, the signal can be used to generate an indication of a particular event, such as the release of body fluids or exudates as in a bandage or personal care product, such as a feminine care product or child care diaper product.

A method used to prepare alumina nanoparticles having functional compounds bonded to the surface included the following steps.

The functional compound was dissolved in water with stirring. To this stirred solution was slowly added the alumina nanoparticles and the resulting mixture stirred for about 5 to 10 minutes to allow the functional compound to bond to the surface of the nanoparticle. The UV-VIS spectrum of the water solution was obtained by taking an aliquot of the stirred mixture and placing it in a quartz cell. The UV-VIS spectra were obtained using a UV-VIS spectrophotometer Model UV-1601 (Shimadzu Corporation) with water as a reference. Zeta Potential and particle size measurements were determined using a ZetaPals Instrument (Brookhaven Instrument Company, Holtsville, NY).

A method used to release the bonded functional compound utilizing a pH trigger included the following steps. The alumina nanoparticle having the functional agent bonded to the surface was placed in an aqueous solution (suspension) with stirring. To this stirred suspension was slowly added dilute sodium hydroxide (0.1N) dropwise and the pH was subsequently measured. An aliquot of this suspension was taken and the UV-VIS spectrum measured. In this manner, the bonded functional agent's Lambda max peak can be observed to decrease with the free functional agent's Lambda max peak observed to appear and increase.

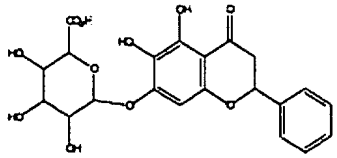
Specific Examples of Adsorption of Various Pharmaceutical or Nutritional Materials to Carrier Nanoparticles:

In a first example of the adsorption of pharmaceutical materials onto the surface of a carrier nanoparticle, the UV-visible absorbance spectrum of Tetracycline was initially measured using a UV-visible spectrophotometer (Perkin-Elmer UV-Visible spectrophotometer.) Tetracycline was found to absorb at 357 nm in water. In particular, 10 mg tetracycline was in 50 ml water. When 5.0 ml SNOWTEX AK suspension 20 % wt/wt (a sol containing silica particles that had an alumina surface coating, as obtained from Nissan Chemical America of Houston, Texas) was added, with stirring, to the tetracycline solution. An aliquot

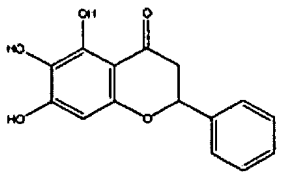
was removed and the UV-VIS spectrum of the solution recorded. A bathochromic shift occurred to give an absorbance of 365 nm, suggesting that the tetracycline had adsorbed onto the alumina surface of SNOWTEX-AK particles. SNOWTEX-AK was initially used in a 50 ml portion of 20% wt/wt suspension. The physical parameters of the SNOWTEX-AK nanoparticles are as follows: SNOWTEX-AK-size :62 nm and Zeta Potential of + 36 mV.In further Examples, additional pharmaceutical agents were evaluated for their propensity to bind strongly to alumina particles. They included the following agents described in Table 1, and which demonstrated the noted shift. These agents are considered antineoplastic for use as drugs that kill or stop the spread of cancer cells. Baicalein has been studied for its antiproliferation effect of human T-lymphoid leukemia cells.

Table 1

SAMPLE	UV-VIS ABSORPTION (nm) FREE AGENT	SN-AK/AGENT
Baicalin Hydrate	278 and 322	295 and 388
Baicalein	320	348
Daunorubicin	472	480



Baicalin Hydrate



Baicalein
(AstringenT)

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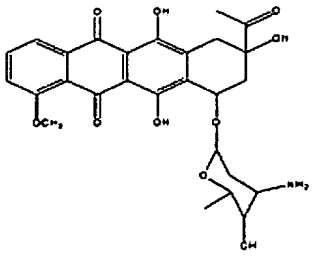

Daunorubicin (Antineoplastic)

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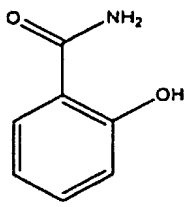
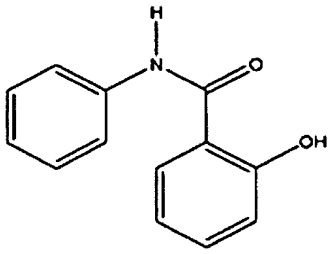
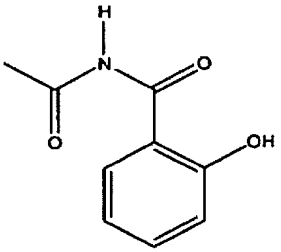
Still additional pharmaceutical agents which may be used in conjunction with this invention include the following materials.



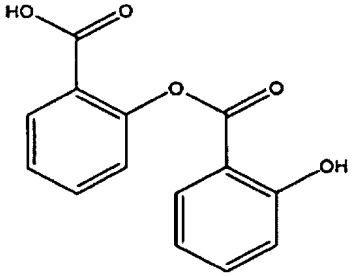
Salicylamide
(Analgesic)



Salicylanilide
(Antifungal)



Salacetamide
(Antipyretic)



Salsalate
(Anti-inflammatory)

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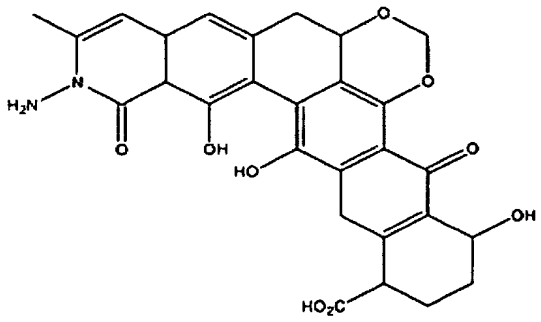
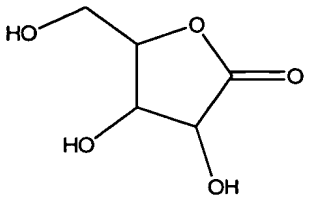


Albofungin
(Antifungal Antibiotic)

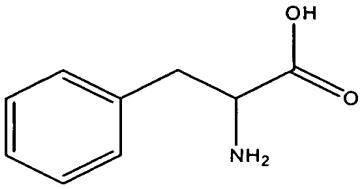
In a similar manner to the previous systems, examples of nutraceutical agents with the desired functional moieties were evaluated for their propensity to

bind to alumina particles. Examples of such compounds were ascorbic acid (Vitamin C) and phenylalanine (sweetener found in Equal®). The structural equations for these materials and their ability to bind to such particles was demonstrated as can be seen in Table 2 which follows:

Table 2



Ascorbic Acid



Phenylalanine

SAMPLE	UV-VIS ABSORPTION (nm)
Ascorbic Acid in water	266
Ascorbic Acid/SN-AK	260
Phenylalanine in water	230
Phenylalanine/SN-AK	224*

*= The structure of the peak changed in addition to the shift.

It should be noted here that a shift in the absorption maximum was observed on addition of SNOWTEX-AK to the ascorbic acid solution, however a blue shift was observed (hypsochromic). This shift was due to binding, as no shift was observed when dilute acid was added to a separate solution of ascorbic acid. In a similar way, a blue shift (hypsochromic shift) was also observed with the phenylalanine binding to SNOWTEX-AK.

Examples of Adsorption of Various Pharmaceutical or Nutritional Materials to Carrier Nanoparticles and the Selective Release of Such Materials Upon Occurrence of a Triggering Mechanism:

In a further set of examples, pharmaceutical materials were adsorbed to carrier alumina particles and then selectively released from the carrier particles. In particular, separate 50 ml Solutions of Tetracycline and hydrocortisone agents (0.01 g) in water were prepared to which the alumina nanoparticle (SNOWTEX-AK) suspension (5 ml of 20% wt/wt) were added. A bathochromic shift (red shift) in the UV-VIS Lambda maxima was again observed, indicating strong binding of these pharmaceutical agents to the surface of the alumina particle. The following Table 3 shows the shift in the UV-VIS spectra recorded. Once the pharmaceutical agents had been bound to particles, they were selectively released by a controlled pH trigger mechanism. Thus, by changing the pH of the modified nanoparticle suspension to high pH values, the pharmaceutical agent was released as observed by a second red shift of the UV-VIS Lambda Maxima. In particular, the alkaline agent , dilute sodium hydroxide (0.1N),was added in 0.5 ml amounts to the samples. The tetracycline was released from the alumina surface when the suspension of modified nanoparticles was altered to pH 9/10 or greater. The noted shifts correspond to the absorption maximum of the free pharmaceutical agents.

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Table 3

SAMPLE	UV-VIS ABSORPTION (nm)
Hydrocortisone in water	241
Hydrocortisone/SN-AK	234
Hydrocortisone/SN-AK with Base	244
Hydrocortisone with base	244
Tetracycline in water	357
Tetracycline/SN-AK	365
Tetracyclin/SN-AK with base	385
Tetracycline with base	385

Therefore, these two examples of pharmaceutical agents demonstrate the capability of selectively releasing pharmaceutical agents from the carrier particles. By the use of a "pH trigger" the functional compounds can be released in a controlled manner when needed. It should be noted that such triggering of the delivery system may be accomplished through environmental changes such as infection which results in pH changes, taking advantage of inherent differences in pH depending on body locations, and the intentional act of introducing chemistries such as pH altering materials to the delivery systems to trigger the release of functional compounds. Chemistries that may be introduced to a delivery system include_bicarbonates, carbonates and buffering salts which would result in a pH change on becoming wet with water or biological fluid. In yet another example, the delivery system would be incorporated into a tampon. Normal healthy vaginal fluid is acidic, typically in the 3-5 pH range. However, when infected with a yeast infection or other microbial infection, the pH changes to the basic range. This swing in pH would trigger the release of medication or buffering agents to restore the healthy pH of the vaginal fluid and flora.

Examples of Signal Systems Which Can be Used to Indicate the Release of Pharmacutical Agents Upon a Change in Environmental Condition:

Silica Particle Binding and Release:

The following examples illustrate the use of silica nanoparticles (as opposed to alumina particles) and the bonding of signal functional agents to the surface of the particles. The pH triggered release for silica coated particles is activated by adding acid and lowering the pH to the environment of the silica particles . Dilute acid is used in these examples.

A method used to prepare silica nanoparticles having functional agents bonded to the surface included the following steps. The functional agent was dissolved into water with stirring. To this stirred solution was slowly added the silica nanoparticles and the resulting mixture stirred for about 5 to10 minutes to allow the functional agent to bond to the surface of the nanoparticles. The UV-VIS spectrum of the water solution was obtained by taking an aliquot of the stirred mixture and placing it in a quartz cell. The UV-VIS spectra were obtained using the

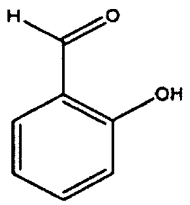
UV-VIS spectrophotometer Model UV-1601 with water as a reference. Zeta Potential and particle size measurements were determined using a ZetaPals Instrument (Brookhaven Instrument Company, Holtsville, NY).

A method used to release the bonded functional agent from the silica surface using a pH trigger included the following steps. The silica nanoparticle having the functional agent bonded to the surface was placed in aqueous solution (suspension) with stirring. To this stirred suspension was slowly added dilute **hydrochloric acid** (0.1N) dropwise and the pH measured. An aliquot of this suspension was taken and the UV-VIS spectrum measured. In this manner, the bonded functional agent's Lambda max peak can be observed to decrease with the free functional agent's Lambda max peak observed to appear and increase.

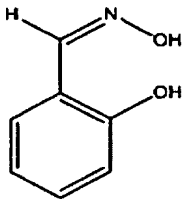
In a similar fashion, the binding of active fragrance compounds to silica nanoparticles (SNOWTEX C, Nissan Chemicals America, Houston, TX) was demonstrated. Accordingly, to a solution (0.01g of salicyclaldehyde in 50 ml of water) of salicylaldehyde (used in the perfume industry as a base fragrance) was added a dilute suspension (3 ml of 2% wt/wt) of silica nanoparticles (Snowtex C, Nissan Chemicals America, Houston TX) with stirring. The UV-VIS absorption of the salicylaldehyde underwent a red shift in its lambda max (see Table 4 below) and the characteristic fragrance disappeared. The red shift is characteristic of the binding of the aryl aldehyde functionality to the silica surface. Upon addition of dilute acid (hydrochloric acid), the aldehyde was released and the fragrance returned. The UV-VIS absorption also underwent a blue shift to return to that of the starting aldehyde. Such chemistry may be used in conjunction with a pharmaceutical to be released upon the change of an environmental condition to indicate/signal that the pharmaceutical material has been delivered. For instance, such signal agent may be adsorbed onto a silica particle. A pharmaceutical compound may be separately adsorbed onto an alumina particle. The particles may be combined and jointly used within a delivery vehicle or as part of a modified drug delivery device. The functional agents then would be triggered upon the occurrence of separate chemical events.

In a similar manner, salicylaldoxime a metal sequestering agent, was also found to bind to the silica particle surface and undergo a pH triggered release. The structural formulas and exemplary data are illustrated in the following Table 4.

Table 4



Salicylaldehyde



Salicylaldoxime

SAMPLE	UV-VIS Absorption (nm) After Addition of Silica	After Addition of Acid
Salicylaldehdye 327nm	382	327
Salicylaldoxime 303nm	350	340

Additionally, a titration study using UV-VIS spectroscopy was carried out to determine the pH at which all of the salicylaldehyde was released. This was found to be at pH 6. In a further alternative embodiment, such nanoparticle delivery systems may be employed to carry the pharmaceutical agent through the stomach (having an acidic environment) and then release the agents into the small intestine (having a basic/alkaline environment). In still another alternative embodiment, such nanoparticle delivery systems may be used as part of a treatment on a tampon for vaginal infections. For instance, a medicated tampon may include a bound antibiotic ("bound" meaning the functional compound adsorbed to the surface of nanoparticles which are themselves attached through charge attraction to a tampon substrate). When the pH of a patient's vagina turns alkaline as a result of a yeast infection, the tampon would be triggered to release the bound antibiotic to control the yeast infection, thereby resulting in the pH returning to the normal acidic environment. In still a further alternative embodiment, such nanoparticle delivery systems may be used as an application to a topical bandage. Upon a change in condition or application of a pH changing chemistry, functional

materials contained on carrier nanoparticles on the bandage can be selectively released into or onto a wound site.

Once any of the above-mentioned functional compounds are bound to the alumina or silica particle (as the case may be) , the particle acts as a delivery vehicle for delivering the functional compound to a desired location. Once bound to the particle, the functional compounds may be easier to handle, may be more stable, or may have other improved properties depending upon the application. Further, the resulting particle structure can be incorporated into various other mediums. For instance, the particle structure can be incorporated into liquid vehicles, can be formed into capsules, can be combined with gels, pastes, other solid materials, and the like, depending on the end-use application.

The particles formed according to the present invention and including the functional compound, can be present in various forms, shapes, and sizes depending upon the desired result. For instance, the particles can be of any shape, for example, a sphere, a crystal, a rod, a disk, a tube, or a string of particles. The size of the particle can also vary dramatically. For instance, in one embodiment, the particles can have an average dimension of less than about 1 mm, particularly less than about 500 microns, and more particularly less than about 100 microns. In other embodiments, however, even smaller sizes may be desired. For instance, the particles can have an average diameter of less than about 1,000 nm, and particularly less than about 500 nm. As used herein, the average dimension of a particle refers to the average length, width, height, or diameter of a particle.

As described above, the particles of the present invention include a surface layer that contains one or more functional compounds. The coating on the particle can be continuous or discontinuous. The particle itself is believed to be amorphous.

In one particular embodiment, compositions made according to the present invention have been found to be well suited to being applied to substrates made from synthetic polymers, such as thermoplastic polymers. Such substrates can include, for instance, woven and non-woven materials made from a polyolefin polymer such as polypropylene or polyethylene, polyester, and the like. In the past, various problems have been experienced in trying to affix materials to these

types of materials. These materials can be particularly effective as drug delivery substrates for delivery through the skin of a patient. The particles of the present invention can be affixed to these materials (as a result of differences in Zeta potential) without the use of chemical binders or complex chemical constructions.

Although not needed, in some embodiments it may be desirable to pre-treat or post-treat the polymer substrates which may further serve to affix the particles to the materials. For instance, substrates made from synthetic polymers can undergo a pretreatment process for increasing the negative surface charge. For example, such pretreatment processes include subjecting the substrate to a corona treatment or to an electret treatment. An electret treatment, for instance, is disclosed in U.S. Patent No. 5,964,926 to Cohen, which is incorporated herein by reference in its entirety. Such pretreatments have been found not only to increase the negative surface charge of polymeric materials, but also assist in wetting out the polymer and enhancing surface adhesion between the polymer and the particles of the present invention.

In addition to pretreatment processes, substrates contacted with the particles of the present invention can also undergo various post treatment processes which further serve to affix the particles to the substrate. For example, in one embodiment, the treated substrate can be subjected to radio frequency radiation or to microwave radiation. Alumina is known to adsorb radio frequency radiation and microwave radiation causing the particles to heat. Once heated, it is believed that the particles become further embedded into the polymeric substrate. Further, the particles can be heated without also heating the substrate to higher than desired temperatures.

Following being affixed to such substrates, upon exposure to a change in condition (such as pH) the functional compounds would be released from the substrate, but the particles would be left behind.

In a specific embodiment, carrier particles (and desirably nanoparticles, that is particles having sizes of less than about 1 micron in size, more desirably between about 5 nm and 500 nm in size, and even more desirably, between about 10 nm – 200 nm in size) including pharmaceutical compounds, can be applied to a topical bandage by various application methods. The application methods may include a gel, a water suspension, a dry coating or a powder placed between the

layers of the bandage. if the particles are included in a vehicle for ease of application. The bandage can then be dried, if appropriate, whereby the charges of the particles would maintain them in close association with the bandage substrate. In this regard, Figure 1 depicts an exploded perspective view of a transdermal drug delivery device in accordance with the invention. Figure 2 depicts a cross-sectional view of the transdermal delivery device of Fig. 1. The transdermal delivery device 70 is designed to deliver a functional agent/compound, either drugs, medicaments, or other treatments, across the skin of a patient's body. The delivery device includes an adhesive layer 72, for affixing the device (patch) to the skin of the patient. The adhesive layer may include a removable protective liner, to protect the adhesive layer during nonuse and also to reduce the likelihood of loss of active ingredient. The adhesive layer may cover the entire lower surface of the transdermal delivery device, or only a peripheral portion of the lower surface, so as not to interfere with the passage of active ingredients across the skin of the consumer. The active ingredient (the coated particle) can be stored in a chamber 82 or in the polymer layer 74. If the active ingredient is stored in a chamber, 82, the polymer layer 74 separates the active ingredient from the adhesive layer. If the active ingredient is in the polymer layer, no chamber is necessary. Such polymer layer 74 may be a single component layer, or alternatively, may comprise two materials (as shown) such as 74 and 80. If the polymer layer is made from two or more distinct polymer components, the medicaments may be targeted to narrower areas of skin, depending upon the ability of each polymer component to allow the passage of the functional compound. The polymer layer is essentially the skin contacting layer, through which the active ingredient passes after the device is applied to the skin of a consumer. The device further includes a backing layer 76, which includes a raised portion 78, for housing the functional compound/active ingredient. The active ingredient is allowed to pass through the polymer layer 74/80 but desirably does not pass through the backing layer 76. The polymer material of the present invention may be utilized as the material for forming a polymer layer in the patch, in order to provide the ability to pass functional compounds to the skin of a user. Such polymer layer may be for example a film (such as a selectively permeable or apertured film) or nonwoven sheet (such as a

spunbond or meltblown, or a combination of such). Such polymer layer may also be in the form of a hydrogel-type material.

While Figures 1 and 2 provide one example of a transdermal delivery device/ bandage, in accordance with the invention, it should be appreciated that numerous variations are contemplated to be within the scope of the invention. For instance, each of the described layers may be constructed of one or more layers for more defined/targeted or efficient health-related compound application. Further, in the case of a bandage, such drug enclosure 82, and separate polymer layer, may in fact be comprised of an absorbent sheet material, such as a nonwoven, that is designed to either retain exudates from a wound site, or to both retain exudates, and also to release moisture or select medicaments that are stored within the absorbent sheet material, upon a change in condition, such as appearance of moisture, body exudates or a change in pH. Such nonwoven web, may be, for instance either a spunbond or meltblown nonwoven web, or a combination of such. In such a fashion, the depicted wound dressing/ transdermal delivery device can function as either a hydrogel or hydrocolloid. Such a dressing could act to donate moisture, absorb exudates, to release functional compound, or a combination of such. Similar polymeric layers can also be part of transmucosal and vaginal delivery devices (tampons), as previously described. Examples of tampon structures are described in U.S. Patent Number 6,177,608, which is hereby incorporated by reference in its entirety.

It should be recognized that the bound pharmaceutical or nutritional chemistry could be used with or without triggerable release. Alternatively, some of the bound chemistry in a multiple chemistry particle system could triggerably releasable, while other bound chemistry could be intentionally retained on the carrier particles. In this fashion, the bound chemistry could perform its advantageous function while still being attached to the carrier particles, for ease of removal or to lower the potential toxicity of the functional agent/compound. An example of such usage would be using a bound salicylaldoxime to remove heavy metals from the body or waste water without the loss of or exposure to the free complexing agent.

In another example, tetracycline could function as an antibiotic while still being bound on a particle. This could allow the antibiotic to function in the

stomach and intestines without crossing over into the bloodstream of a patient (because of the size of the particle). This control of the antibiotic release could assist with lowering the risk of sensitization of patients who are allergic to such medications.

These and other modifications and variations to the present invention may be practiced by those of ordinary skill in the art, without departing from the spirit and scope of the present invention, which is more particularly set forth in the appended claims. In addition, it should be understood that aspects of the various embodiments may be interchanged both in whole or in part. Furthermore, those of ordinary skill in the art will appreciate that the foregoing description is by way of example only, and is not intended to limit the invention so further described in such appended claims.